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(54) **EPOTHILON-NEBENKOMPONENTEN**
EPOTHILONE MINOR CONSTITUENTS
CONSTITUANTS SECONDAIRES D'EPOTHILONE

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(73) Patentinhaber: **Gesellschaft für Biotechnologische Forschung mbH (GBF)**
38124 Braunschweig (DE)

(72) Erfinder:
- **HOEFLE, Gerhard**
  D-38124 Braunschweig (DE)
- **REICHENBACH, Hans**
  D-38124 Braunschweig (DE)
- **GERTH, Klaus**
  D-38124 Braunschweig (DE)
- **HARDT, Ingo**
  D-38124 Braunschweig (DE)
- **SASSE, Florenz**
  D-38124 Braunschweig (DE)
- **STEINMETZ, Heinrich**
  D-38124 Braunschweig (DE)

(74) Vertreter: **Boeters, Hans Dietrich, Dr. et al**
Patentanwälte Boeters & Bauer,
Bereiteranger 15
81541 München (DE)

(56) Entgegenhaltungen:
WO-A-97/19086 **WO-A-98/08849**
WO-A-98/22461

- **NICOLAOU K C ET AL: "DESIGNED EPOTHILONES: COMBINATORIAL SYNTHESIS, TUBULIN ASSEMBLY PROPERTIES, AND CYTOTOXIC ACTION AGAINST TAXOL.RESISTANT TUMOR CELLS" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION,DE,VERLAG CHEMIE. WEINHEIM, Bd. 36, Nr. 19, 1. Januar 1997 (1997-01-01), Seiten 2097-2103, XP002064441 ISSN: 0570-0833**
- **NICOLAOU ET AL: "Total synthesis of oxazole- and cyclopropane-containing epothilone A analogs by the olefin metathesis approach" CHEMISTRY - A EUROPEAN JOURNAL,US,VCH PUBLISHERS, Bd. 3, Nr. 12, 1997, Seiten 1957-1970, XP002121565 ISSN: 0947-6539**
- **BALOG A ET AL: "Stereoselective Syntheses and Evaluation of Compounds in the 8-Desmethylepothilone A Series: Some Surprising Observations Regarding Their Chemical and Biological Properties" TETRAHEDRON LETTERS,NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, Bd. 38, Nr. 26, 30. Juni 1997 (1997-06-30), Seiten 4529-4532, XP004074826 ISSN: 0040-4039**
- **SU D -S ET AL: "STRUCTURE - ACTIVITY RELATIONSHIPS OF THE EPOTHILONES AND THE FIRST IN VIVO COMPARISON WITH PACLITAXEL" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION,DE,VERLAG CHEMIE. WEINHEIM, Bd. 36, Nr. 19, 1997, Seiten 2093-2096, XP002916075 ISSN: 0570-0833**

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(Forts. nächste Seite)

EP 1 087 975 B1

- K.C. NICOLAOU ET AL.: "Probing the ring size of epothilones: total synthesis of [14]-, [15]-, [17]-, and [18]Epothilones A" ANGEWANDTE CHEMIE INTERNATIONAL EDITION., Bd. 37, Nr. 1/2, 1998, Seiten 81-84, XP002131226 WEINHEIM DE

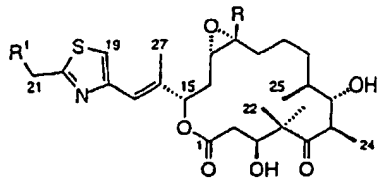
Beschreibung

[0001] Die Erfindung betrifft Verbindungen, die im vorliegenden Zusammenhang als Epothilon-Nebenkomponenten bezeichnet werden, und zwar Verbindungen 5 bis 7, 16 bis 19, 26 und 28 bis 29. Diese Verbindungen lassen sich durch Fermentation von DSM 6773 gemäß DE 41 38 042.8 gewinnen.

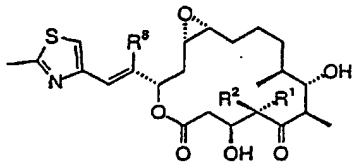
[0002] Kenndaten der erfindungsgemäßen Verbindungen sind im folgenden zusammengestellt.

[0003] Gewinnung: Die Aufarbeitung eines Rohepothilon-Gemischs, das durch Fermentation von DSM 6773 in einem 900 Liter-Fermentator gewonnen wurde, ist schematisch Fig. 1 bis 2 zu entnehmen.

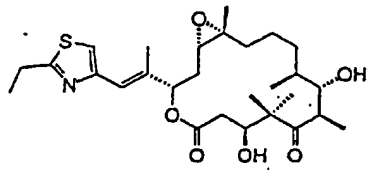
[0004] Aktivitäten: vgl. Tab. 1



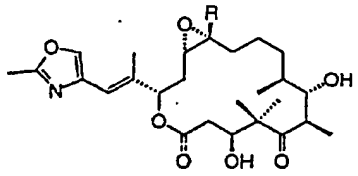
Epothilone A (1) R^1 = H; R = H
Epothilone B (2) R^1 = H; R = Me
Epothilone E (3) R^1 = OH; R = H
Epothilone F (4) R^1 = OH; R = Me



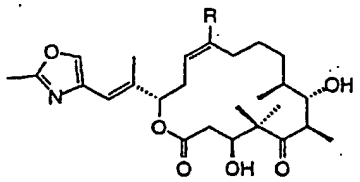
Epothilone A_1 (5) R^1 = H; R^2, R^8 = Me
Epothilone A_2 (6) R^2 = H; R^1, R^8 = Me
Epothilone A_8 (7) R^8 = H; R^1, R^2 = Me
Epothilone A_9 (8) R^1 = CH_2OH; R^2, R^8 = Me



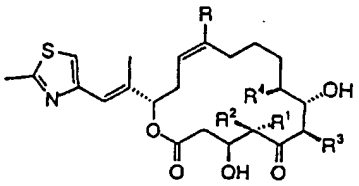
Epothilone B_{10} (9)



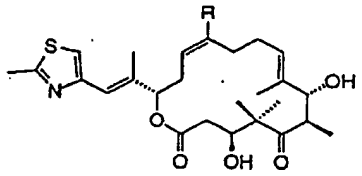
Epothilone G_1 (10) R = H
Epothilone G_2 (11) R = Me



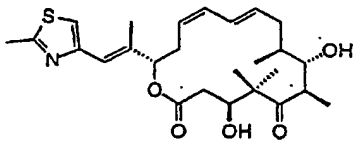
Epothilone H_1 (12) R = H
Epothilone H_2 (13) R = Me



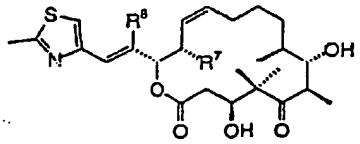
Epothilone C (14) R^1, R^2, R^3, R^4 = Me; R = H
Epothilone D (15) R^1, R^2, R^3, R^4, R = Me
Epothilone C_1 (16) R^1 = H; R^2, R^3, R^4 = Me; R = H
Epothilone D_1 (17) R^1 = H; R^2, R^3, R^4 = Me; R = [illegible]
Epothilone C_2 (18) R^2 = H; R^1, R^3, R^4 = Me; R = H
Epothilone D_2 (19) R^2 = H; R^1, R^3, R^4 = Me; R = [illegible]
Epothilone C_3 (20) R^3 = H; R^1, R^2, R^4 = Me; R = H
Epothilone C_4 (21) R^4 = H; R^1, R^2, R^3 = Me; R = H



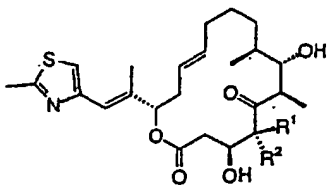
Epothilone C_5 (22) R = H
Epothilone D_5 (23) R = Me



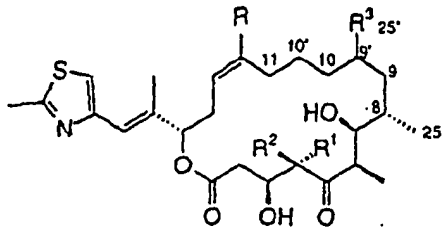
Epothilone C_6 (24)



Epothilone C_7 (25) R^7 = OH; R^8 = Me
Epothilone C_8 (26) R^8, R^7 = H
Epothilone C_9 (27) R^8 = CH_2OH; R^7 = H



trans-Epothilone C_1 (28) R^1 = H; R^2 = Me
trans-Epothilone C_2 (29) R^2 = H; R^1 = Me



Epothilone I_1 (30) R, R^3 = H; R^1, R^2 = Me

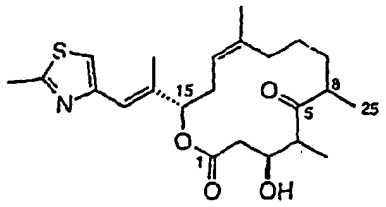
Epothilone I_2 (31) R = H; R^1, R^2, R^3 = Me

Epothilone I_3 (32) R^1, R^2, R^3, R = Me

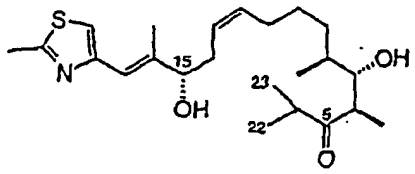
Epothilone I_4 (33) R^2, R = H; R^1, R^3 = Me

Epothilone I_5 (34) R^2 = H; R^1, R^3, R = Me

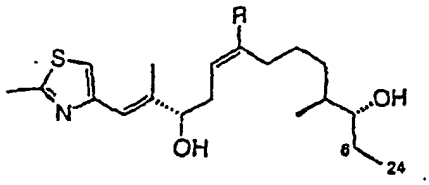
Epothilone I_6 (35) R^1 = H; R^2, R^3, R = Me



Epothilone K (36)



(37)



(38) R = H

(39) R = Me

Epothilone A_1 (5): colorless amorphous solid; $[\alpha]^{22}_D$ -69 (*c* 0.1, MeOH); UV (MeOH) λ_{max} nm (ε) 208 (19600), 247 (13600); IR (KBr) ν_{max} 3437, 2959, 2931, 2876, 1732, 1710, 1455, 1259, 978 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.95 (1H, s, H-19), 6.60 (1H, bs, H-17), 5.68 (1H, dd, *J*= 4.4, 4.0 Hz, H-15), 4.12 (1H, m, H-3), 3.71 (1H, m, H-7), 3.52 (1H, bs, 7-OH), 3.37 (1H, bd, *J*= 7.5 Hz, 3-OH), 3.21 (1H, dq, *J* = 7.7, 7.0 Hz, H-4), 3.02 (1H, ddd, *J* = 9.2, 4.5, 2.8 Hz, H-13), 2.87 (1H, ddd, *J* = 8.3, 4.5, 3.7 Hz, H-12), 2.78 (1H, dd, *J* = 16.8, 4.3 Hz, H-2a), 2.70 (3H, s, H-21), 2.66 (1H, dq, *J*= 3.9, 7.0 Hz, H-6), 2.65 (1H, dd, *J* = 16.8, 5.2 Hz, H-2b), 2.16 (1H, ddd, *J*= 15.4, 4.4, 2.8 Hz, H-14a), 2.12 (3H, bs, H-27), 1.91 (1H, ddd, *J*= 15.4, 9.2, 4.0 Hz, H-14b), 1.63 (1H, m, H-10a), 1.62 (2H, m, H-11), 1.59 (1H, m, H-9a), 1.52 (1H, m, H-10b), 1.39 (1H, m, H-8), 1.35 (1H, m, H-9b), 1.211 (3H, d, *J*= 7.0 Hz, H-23), 1.207 (3H, d, *J* = 7.0 Hz, H-24), 0.89 (3H, d, *J*= 6.9 Hz, H-25); EIMS *m/z* 479 $[M]^+$ (21), 322 (31), 306 (65), 304 (47), 168 (45), 166 (73), 164 (100), 151 (30). 140 (35); HREIMS *m/z* 479.2317 (calcd. for $C_{27}H_{41}NO_5S$, 479.2342).

Epothilone A_2 (6): colorless amorphous solid; $[\alpha]^{22}_D$ +12.0 (*c* 1.0, MeOH); UV (MeOH) λ_{max} nm (ε) 210 (15100), 248 (15500); IR (KBr) ν_{max} 3438, 2963, 2929, 2875, 1734, 1706, 1458, 1262, 981 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.98 (1H, s, H-19), 6.63 (1H, bs, H-17), 5.40 (1H, dd, *J* = 8.3, 3.4 Hz, H-15), 4.26 (1H, ddd, *J*= 8.5, 4.8, 4.7 Hz, H-3), 3.85 (1H, dd, *J*= 7.9, 2.6 Hz, H-7), 3.54 (1H, bs, 3-OH), 3.09 (1H, dq, *J*= 4.8, 7.0 Hz, H-4), 3.01 (1H, ddd, *J* = 8.3, 4.8, 4.6 Hz, H-13), 2.98 (1H, dq, *J* = 7.9, 7.0 Hz, H-6), 2.89 (1H, ddd, *J*= 6.7, 4.6, 4.4 Hz, H-12), 2.68 (3H, s, H-21), 2.60 (1H, dd, *J* = 15.1, 8.5 Hz, H-2a), 2.52 (1H, bs, 7-OH), 2.50 (1H, dd, *J* = 15.1, 4.7 Hz, H-2b), 2.18 (1H, ddd, *J*= 15.0, 4.8, 3.4 Hz, H-14a), 2.11 (3H, d, *J* = 1.3 Hz, H-27), 1.82 (1H, ddd, *J* = 15.0, 8.3, 8.1 Hz, H-14b), 1.63 (1H, m, H-8), 1.61 (2H, m, H-11a and H-10a), 1.46(1H, m, H-11b), 1.39 (2H, m, H-9), 1.31 (1H, m, H-10b), 1.22 (3H, *d*, *J* = 7.0 Hz, H-24), 1.15 (3H, d, *J* = 7.0 Hz, H-22), 1.01 (3H, d, *J* = 6.9 Hz, H-25); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 216.2 (s, C-5), 170.1 (s, C-1), 164.9 (s, C-20), 152.0 (s, C-18), 137.0 (s, C-16), 120.3 (d, C-17), 116.5 (d, C-19), 76.7 (d, C-15), 75.6 (d, C-7), 69.1 (d, C-3), 57.1 (d, C-12), 54.3 (d, C-13), 50.3 (d, C-4), 49.6 (d, C-6), 39.4 (t, C-2), 35.5 (d, C-8), 32.2 (t, C-14), 29.6 (t, C-9), 27.6 (t, C-11), 23.9 (t, C-10), 19.2 (q, C-21), 18.0 (q, C-25), 15.6 (q, C-27), 13.9 (q, C-24), 12.4 (q, C-22); EIMS *m/z* 479 $[M]^+$ (18), 322 (38), 306 (78), 304 (59), 168 (48), 166 (96), 164 (100), 151 (33), 140 (38); HREIMS *m/z* 479.2318 (calcd. for $C_{27}H_{41}NO_5S$, 479.2342).

Epothilone A_8 (7): colorless amorphous solid; $[\alpha]^{22}_D$ -76.2 (*c* 1.0, MeOH); UV (MeOH) λ_{max} nm (ε) 210 (15300), 248 (15500); IR (KBr) ν_{max} 3440, 2967, 2932, 2876, 1736, 1691, 1467, 1252, 979 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.95 (1H, s, H-19), 6.64 (1H, dd, *J* = 15.6, 0.9 Hz, H-17), 6.52 (1H, dd, *J* = 15.6, 6.6 Hz, H-16), 5.68 (1H, dddd, *J* = 7.8, 6.6, 3.2, 0.9 Hz, H-15), 4.11 (1H, ddd, *J* = 10.1, 6.6, 3.5 Hz, H-3), 3.78 (1H, ddd, *J* = 5.2, 3.2, 3.2 Hz, H-7), 3.66 (1H, d, *J* = 6.6 Hz, 3-OH), 3.23 (1H, dq, *J* = 5.2, 6.9 Hz, H-6), 3.08 (1H, ddd, *J* = 7.3, 5.5,4.1 Hz, H-13), 2.90 (1H, ddd, *J*= 6.6, 4.6, 4.1 Hz, H-12), 2.69 (3H, s, H-21), 2.52 (1H, dd, *J* = 14.7, 10.1 Hz, H-2a), 2.44 (1H, bd, *J* = 3.2 Hz, 7-OH), 2.41 (1H, dd, *J* = 14.7, 3.5 Hz, H-2b), 2.10 (1H, ddd, *J* = 15.0, 5.5, 3.2 Hz, H-14a), 1.90 (1H, ddd, *J* = 15.0, 7.8, 7.3 Hz, H-14b), 1.71 (1H, m, H-8), 1.65 (1H, m, H-11a), 1.50 (1H, m, H-10a), 1.47 (1H, m, H-11b), 1.40 (2H, m, H-9), 1.39 (1H, m, H-10b), 1.33 (3H, s, H-23), 1.16 (3H, d, *J* = 6.9 Hz, H-24), 1.08 (3H, s, H-22), 0.98 (3H, d, *J* = 7.0 Hz, H-25); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 220.3 (s, C-5), 170.7 (s, C-1), 166.5 (s, C-20), 152.2 (s, C-18), 128.4 (d, C-16), 125.9 (d, C-17), 116.4 (d, C-19), 75.0 (d, C-7), 73.6 (d, C-3), 72.7 (d, C-15), 57.3 (d, C-12), 54.1 (d, C-13), 52.6 (s, C-4), 43.8 (d, C-6), 38.9 (t, C-2), 36.3 (d, C-8), 32.5 (t, C-14), 30.3 (t, C-9), 26.7 (t, C-11), 24.0 (t, C-10), 21.3 (q, C-23), 21.0 (q, C-22), 19.3 (q, C-21), 17.1 (q, C-25), 14.5 (q, C-24); EIMS *m/z* 479 $[M]^+$; HRDCIMS *m/z* 480.2401 (calcd. for $C_{25}H_{38}NO_6S$, 480.2401).

Epothilone C_1 (16): colorless amorphous solid; $[\alpha]^{22}_D$ -114.0 (*c* 10.0, MeOH); UV (MeOH) λ_{max} nm (ε) 211 (16500), 248 (12500); IR (KBr) ν_{max} 3440, 2933, 2877, 2858, 1730, 1708, 1457, 1244, 981 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.96 (1H, s, H-19), 6.56 (1H, bs, H-17), 5.47 (1H, dd, *J* = 9.2, 3.0 Hz, H-15), 5.43 (1H, m, H-12), 5.40 (1H, m, H-13), 4.40 (1H, ddd, *J* = 6.2, 6.1, 6.1 Hz, H-3), 3.69 (1H, dd, *J* = 5.7, 3.6 Hz, H-7), 3.01 (1H, dq, *J* = 5.7, 6.9 Hz, H-6), 3.01 (1H, bs, 3-OH), 2.84 (1H, dq, *J* = 5.2, 7.0 Hz, H-4), 2.68 (3H, s, H-21), 2.66 (1H, ddd, *J* = 16.4, 9.2, 7.3 Hz, H-14a), 2.64 (1H, dd, *J* = 15.9, 7.1 Hz, H-2a), 2.54 (1H, dd, *J* = 15.9, 6.1 Hz, H-2b), 2.38 (1H, bd, *J* = 16.4 Hz, H-14b), 2.35 (1H, bs, 7-OH), 2.07 (3H, bs, H-27), 2.03 (2H, m, H-11), 1.62 (1H, m, H-10a), 1.53 (1H, m, H-8), 1.35 (1H, m, H-9a), 1.22 (1H, m, H-9b), 1.19 (3H, d, *J* = 6.9 Hz, H-24), 1.14 (3H, d, *J* = 6.9 Hz, H-23), 1.10 (1H, m, H-10b), 0.95 (3H, d, *J* = 6.9 Hz, H-25); ^{13}C NMR, see Table 1; EIMS *m/z* 463 $[M]^+$ (5), 324 (8), 290 (8), 204 (7), 168 (100), 164 (15), 139 (36); HREIMS *m/z* 463.2381 (calcd. for $C_{25}H_{37}NO_5S$, 463.2392).

Epothilone D_1 (17): colorless amorphous solid; $[\alpha]^{22}_D$ -118.6 (*c* 0.5, MeOH); UV (MeOH) λ_{max} nm (ε) 208 (18300), 249 (11900); IR (KBr) ν_{max} 3439, 2965, 2934, 2877, 1729, 1707, 1456, 1250, 980 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.98 (1H, s, H-19), 6.56 (1H, bs, H-17), 5.51 (1H, dd, *J* = 9.5, 3.4 Hz, H-15), 5.16 (1H, dd, *J* = 8.0, 4.2 Hz, H-13), 4.42 (1H, ddd, *J* = 7.1, 6.3, 5.5 Hz, H-3), 3.70 (1H, dd, *J* = 6.5, 2.9 Hz, H-7), 3.07 (1H, dq, *J* = 6.5, 6.9 Hz, H-6), 2.95 (1H, dq, *J* = 4.7, 7.0 Hz, H-4), 2.71 (3H, s, H-21), 2.69 (1H, dd, *J* = 16.0, 6.3 Hz, H-2a), 2.64 (1H, m, H-14a), 2.59 (1H, dd, *J* = 16.0, 7.1 Hz, H-2b), 2.46 (1H, bs, 3-OH), 2.38 (1H, bd, *J*= 16.0 Hz, H-14b), 2.19 (1H, ddd, *J* = 13.3, 8.6, 5.7 Hz, H-11a), 2.10 (3H, d, *J* = 1.4 Hz, H-27), 2.02 (1H, bs, 7-OH), 1.91 (1H, ddd, *J* = 13.3, 6.0, 6.0 Hz, H-11b), 1.68 (1H, m, H-10a), 1.66 (3H, bs, H-26), 1.53 (1H, m, H-8), 1.37 (1H, m, H-9a), 1.26 (1H, m, H-9b), 1.24 (3H, d, *J* = 6.9 Hz, H-24), 1.19 (1H, m, H-10b), 1.14 (3H, d. *J* = 7.0, H-23), 0.99 (3H, d, *J* = 6.9 Hz, H-25); ^{13}C

NMR ($CDCl_3$, 100 MHz) δ 217.0 (s, C-5), 169.7 (s, C-1), 165.0 (s, C-20), 152.2 (s, C-18), 138.5 (s, C-12), 137.7 (s, C-16), 120.7 (d, C-13), 120.1 (d, C-17), 116.3 (d, C-19), 78.8 (d, C-15), 77.2 (d, C-7), 67.7 (d, C-3), 52.1 (d, C-4), 46.5 (d, C-6), 40.6 (t, C-2), 37.6 (d, C-8), 32.3 (t, C-14), 31.8 (t, C-11), 29.5(t, C-9), 25.5 (t, C-10), 23.1 (q, C-26), 19.2 (q, C-21), 15.5 (q, C-27), 16.6 (q, C-25), 14.5 (q, C-24), 9.7 (q, C-23); EIMS *m/z* 477 $[M]^+$ (13), 304 (19), 303 (31), 218 (40), 204 (41), 168 (100), 164 (45), 157 (25), 139 (18); HREIMS *m/z* 477.2544 (calcd. for $C_{26}H_{39}NO_5S$, 477.2549).

Epothilone C_2 (18): colorless amorphous solid; $[\alpha]^{22}_D$ -11.6 (*c* 10.0, MeOH); UV (MeOH) λ_{max} nm (ε) 212 (15500), 249 (12100); IR (KBr) ν_{max} 3428, 2962, 2929, 2877, 2859, 1734, 1705, 1460, 1251, 982 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.99 (1H, s, H-19), 6.66 (1H, bs, H-17), 5.55 (1H, ddd, *J* = 10.4, 9.2, 6.1 Hz, H-12), 5.38 (1H, ddd, *J* = 10.4, 9.3, 6.2 Hz, H-13), 5.22 (1H, dd, *J* = 8.8, 2.8 Hz, H-15), 4.42 (1H, dddd, *J* = 9.4, 5.6, 4.2, 4.1 Hz, H-3), 3.93 (1H, d, *J* = 5.6 Hz, 3-OH), 3.86 (1H, m, H-7), 3.15 (1H, bs, 7-OH), 3.12 (1H, dq, *J* = 4.2, 7.0 Hz, H-4), 3.00 (1H, dq, *J* = 6.9, 7.0 Hz, H-6), 2.70 (3H, s, H-21), 2.62 (1H, dddd, *J* = 15.1, 9.3, 8.8, 0.8 Hz, H-14a), 2.58 (1H, dd, *J* = 15.4, 9.4 Hz, H-2a), 2.38 (1H, dd, *J* = 15.4, 4.1 Hz, H-2b), 2.31 (1H, ddd, *J* = 15.1, 6.2, 2.8 Hz, H-14b), 2.08 (3H, d, *J* = 1.3 Hz, H-27), 2.15 (1H, m, H-11a), 2.04 (1H, m, H-11b), 1.71 (1H, m, H-10a), 1.43 (1H, m, H-9a), 1.31 (1H, m, H-9b), 1.26 (3H, d, *J* = 7.0 Hz, H-24), 1.15 (3H, d, *J* = 7.0 Hz, H-23), 1.11 (1H, m, H-10b), 1.00 (3H, d, *J* = 6.9 Hz, H-25); ^{13}C NMR, see Table 1; EIMS *m/z* 463 $[M]^+$ (7), 324 (7), 306 (8), 290 (17), 168 (100), 164 (14), 139 (27); HREIMS *m/z* 463.2392 (calcd. for $C_{25}H_{37}NO_5S$, 463.2392).

Epothilone D_2 (19): colorless amorphous solid; $[\alpha]^{22}_D$-12.5 (*c* 1.0, MeOH); UV (MeOH) λ_{max} nm (ε) 210 (15400), 248 (11200); IR(KBr) ν_{max} 3436, 2965, 2930, 2877, 1732, 1705, 1458, 1253, 980 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.97 (1H, s, H-19), 6.56 (1H, bs, H-17), 5.18 (1H, dd, *J*= 7.9, 4.9 Hz, H-15), 5.18 (1H, ddd, *J* = 9.6, 5.4, 1.0 Hz, H-13), 4.27 (1H, m, H-3), 3.88 (1H, dd, *J* = 5.6, 4.6 Hz, H-7), 3.19 (1H, bs, 3-OH), 3.07 (1H, dq, *J* = 4.3, 7.0 Hz, H-4), 2.95 (1H, dq, *J* = 5.6, 7.0 Hz, H-6), 2.70 (3H, s, H-21), 2.62 (1H, dd, *J* = 14.9, 7.8 Hz, H-2a), 2.56 (1H, ddd, *J* = 14.7, 9.6, 7.9 Hz, H-14a), 2.43 (1H, dd, *J* = 14.9, 5.6 Hz, H-2b), 2.38 (1H, bs, 7-OH), 2.26 (1H, ddd. *J* = 14.5, 5.4, 4.9 Hz, H-14b), 2.19 (1H, ddd, *J* = 13.0, 10.4, 5.4 Hz, H-11a), 2.10 (3H, d, *J* = 1.4 Hz, H-27), 1.95 (1H, ddd, *J* = 13.0, 10.3, 5.3 Hz, H-11b), 1.72 (1H, m, H-8), 1.68 (3H, bs, H-26), 1.61 (1H, m, H-10a), 1.39 (2H, m, H-9), 1.21 (1H, m, H-10b), 1.19 (3H, d, *J* = 6.9 Hz, H-24), 1.17 (3H, d. *J* = 7.0, H-22), 1.00 (3H, d, *J* = 6.9 Hz, H-25); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 216.8 (s, C-5), 170.4 (s, C-1), 164.9 (s, C-20), 152.3 (s, C-18), 139.8 (s, C-12), 137.5 (s, C-16), 120.5 (d, C-17), 119.2 (d, C-13), 116.3 (d, C-19), 80.0 (d, C-15), 74.3 (d, C-7), 69.7 (d, C-3), 48.6 (d, C-4), 48.4 (d, C-6), 39.9 (t, C-2), 36.6 (d, C-8), 32.2 (t, C-14), 32.7 (t, C-11), 30.9 (t, C-9), 26.0 (t, C-10), 23.6 (q, C-26), 19.2 (q, C-21), 15.4 (q, C-27), 17.1 (q, C-25), 12.4 (q, C-24),12.7 (q, C-23); EIMS *m/z* 477 $[M]^+$ (22), 304 (19), 303 (17), 218 (22), 204 (25), 168 (100), 164 (28), 157 (31), 139 (21); HREIMS *m/z* 477.2545 (calcd. for $C_{26}H_{39}NO_5S$, 477.2549).

Epothilone C_8 (26): colorless amorphous solid; $[\alpha]^{22}_D$-75.2 (*c* 2.5, MeOH]; UV (MeOH) λ_{max} nm (ε) 210 (16800), 248 (17800); IR (KBr) ν_{max} 3443, 2932, 2881, 1734, 1689, 1465, 1255, 1183, 976 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.93 (1H, s, H-19), 6.62 (1H, dd, *J* = 15.6, 0.6 Hz, H-17), 6.49 (1H, dd, *J* = 15.6, 6.6 Hz, H-16), 5.52 (1H, dddd, *J* = 9.5, 6.6, 2.8, 0.6 Hz, H-15), 5.42 (1H, m, H-12), 5.41 (1H, m, H-13), 4.13 (1H, ddd, *J* = 11.0, 5.3, 2.8 Hz, H-3), 3.69 (1H, ddd, *J* = 3.7, 2.8, 2.5 Hz, H-7), 3.11 (1H, dq, *J* = 2.5, 6.8 Hz, H-6), 2.95 (1H, d, *J* = 5.3 Hz, 3-OH), 2.90 (1H, d, *J* = 2.8 Hz, 7-OH), 2.69 (3H, s, H-21), 2.67 (1H, ddd, *J* = 14.9, 9.5, 8.4 Hz, H-14a), 2.48 (1H, dd, *J* = 15.6, 11.0 Hz, H-2a), 2.33 (1H, dd, *J* = 15.6, 2.8 Hz, H-2b), 2.30 (1H, bd, *J* = 14.9 Hz, H-14b), 2.14 (1H, m, H-11a), 2.03 (1H, m, H-11b), 1.71 (1H, m, H-8), 1.63 (1H, m, H-10a), 1.31 (1H, m, H-9a), 1.29 (3H, s, H-23), 1.17 (3H, d, *J* = 6.8 Hz, H-24), 1.16 (1H, m, H-10b), 1.14 (1H, m, H-9b), 1.05 (3H, s, H-22), 0.97 (3H, d, *J* = 7.1 Hz, H-25); ^{13}C NMR, see Table 1; EIMS *m/z* 463 $[M]^+$ (21), 310 (10), 276 (21), 171 (83), 154 (100), 150 (27), 111 (18); HREIMS *m/z* 463.2382 (calcd. for $C_{25}H_{37}NO_5S$, 463.2392).

trans-Epothilone C_1 (28): colorless amorphous solid; $[\alpha]^{22}_D$ -84 (c 0.2, MeOH); UV (MeOH) λ_{max} nm (ε) 211 (17400), 248 (12900); IR (KBr) ν_{max} 3433, 2961, 2933, 2879, 1730, 1708, 1457, 1251, 975 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.00 (1H, s, H-19), 6.64 (1H, bs, H-17), 5.45 (1H, ddd, *J* = 15.2, 6.5, 6.5 Hz, H-12), 5.42 (1H, dd, *J* = 6.4, 3.7 Hz, H-15), 5.35 (1H, dt, *J* = 15.2, 7.1 Hz, H-13), 4.42 (1H, m, H-3), 3.58 (1H, ddd, *J* = 8.1, 7.9, 2.8 Hz, H-7), 3.24 (1H, m, H-6), 3.14 (1H, dq, *J* = 4.0, 6.9 Hz, H-6), 2.92 (1H, d, *J* = 7.9 Hz, 7-OH), 2.71 (3H, s, H-21), 2.71 (2H, m, H-2), 2.53 (2H, m, H-14), 2.17 (1H, d, *J* = 2.17 Hz, 3-OH), 2.11 (1H, m, H-11a), 2.06 (3H, bs, H-27), 1.93 (1H, m, H-11b), 1.68 (1H, m, H-9a), 1.65 (1H, m, H-10a), 1.33 (1H, m, H-8), 1.26 (3H, d, *J* = 6.8 Hz, H-24), 1.16 (1H, m, H-10b), 1.12 (3H, d, *J* = 6.9 Hz, H-22), 1.07 (1H, m, H-9b), 1.00 (3H, d, *J* = 6.8 Hz, H-25); ^{13}C NMR, see Table 1; EIMS *m/z* 463 $[M]^+$ (6), 290 (21), 289 (20), 204 (23), 194 (19), 190 (22), 168 (100), 164 (48), 157 (14), 152 (19), 151 (17), 139 (15), 111 (18); HREIMS *m/z* 463.2371 (calcd. for $C_{25}H_{37}NO_5S$, 463.2392).

trans-Epothilone C_2 (29): colorless amorphous solid; $[\alpha]^{22}_D$ -3 (*c* 1.5, MeOH); UV (MeOH) λ_{max} nm (ε) 211 (15800), 248 (11900); IR (KBr) ν_{max} 3435, 2963, 2931, 2878, 1731, 1706, 1457, 1273, 979 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 6.99 (1H, s, H-19), 6.57 (1H, bs, H-17), 5.56 (1H, ddd, *J* = 15.1, 7.4, 7.0 Hz, H-12), 5.41 (1H, ddd, *J* = 15.1, 7.0, 6.9 Hz, H-13), 5.41 (1H, dd, *J* = 7.7, 2.8 Hz, H-15), 4.13 (1H, dddd, *J* = 6.7, 6.2, 5.6, 5.1 Hz, H-3), 3.78 (1H, ddd, *J* = 8.2, 6.5, 1.9 Hz, H-7), 3.18 (1H, d, *J* = 5.6 Hz, 3-OH), 3.06 (1H, dq, *J*= 8.2, 7.1 Hz, H-6), 2.98 (1H,

dq, J = 6.2, 7.0 Hz, H-4), 2.71 (3H, s, H-21), 2.64 (1H, dd, J = 15.1, 6.7 Hz, H-2a), 2.54 (1H, dd, J = 15.1, 5.1 Hz, H-2b), 2.44 (2H, m, H-14), 2.22 (1H, dddd, J = 13.8, 7.0, 6.2, 2.9 Hz, H-11a), 2.10 (3H, d, J = 1.1 Hz, H-27), 2.09 (1H, d, J= 6.5 Hz, 7-OH), 1.88 (1H, dddd, J = 13.8, 10.9, 7.4, 2.9 Hz, H-11b), 1.65 (1H, m, H-8), 1.63 (1H, m, H-10a), 1.56 (1H, dddd, J = 12.7, 12.7, 3.9, 3.9 Hz, H-9a), 1.20 (3H, d, J = 7.1 Hz, H-24), 1.15 (3H, d, J = 7.0 Hz, H-23), 1.13 (1H, m, H-10b), 1.04 (1H, m, H-9b), 1.01 (3H, d, J = 7.0 Hz, H-25); ^{13}C NMR, see Table 1; EIMS *m/z* 463 $[M]^+$ (13), 290 (11), 190 (10), 168 (100), 164 (20), 157 (26), 139 (17); HREIMS *m/z* 463.2383 (calcd. for $C_{25}H_{37}NO_5S$, 463.2392).

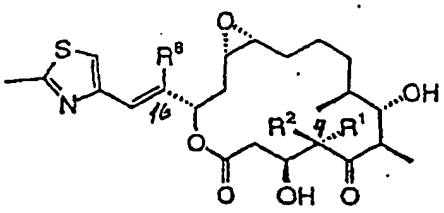
Tab 1.

Aktivität von Epothilonen und Verbindungen (1) bis (39) gegen gegen Maus-Fibroblasten (L929, IC50 /ng/ml/)

Strukturtyp	Epothilone				
	A_Y	B_Y	C_Y	D_Y	trans C_Y
Ausgangsepothilon	(1) 4	(2) 1-2	(14) 50-100	(15) 20	-
21-Hydroxy (E&F)	(3) 10	(4) 1.5	-	-	-
Oxazoles (G&H)	(10) 6	(11) 1	(12) 120	(13) 11	-
(*R*)-4-Desmethyl (X_1)	(5) 20	-	(16) 200	(17) 20	(28) 400
(*S*)-4-Desmethyl (X_2)	(6) 7	-	(18) 25-30	(19) 12	(29) 80
6-Desmethyl (X_3)	-	-	(20) 1500	-	-
8-Desmethyl (X_4)	-	-	(21) 800	-	-
8,9-Dehydro (X_5)	-	-	(22) 1500	(23) 200	-
10,11-Dehydro (X_6)	-	-	(24) 120	-	-
14-Hydroxy (X_7)	-	-	(25)	-	-
16-Desmethyl (X_8)	(7) 20	-	(26) 250	-	-
27-Hydroxy (X_9)	(8) 100	-	(27) 200	-	-
21-Methyl (X_{10})	-	(9) 1.5	-	-	-
Verbindung	-	-	(36) 180		
Verbindung	-	-	(37) 50	-	-
Verbindung	-	-	(38) 2000	(39) 500	-

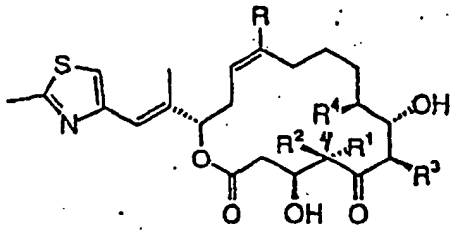
Patentansprüche

1. Epothilon der Formel



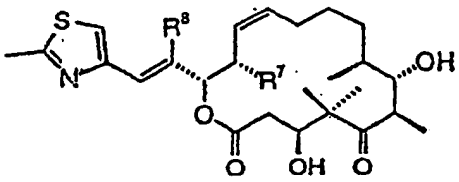
Epothilone A_1 (5) R^1 = H; R^2, R^8 = Me oder
Epothilone A_2 (6) R^2 = H; R^1, R^8 = Me oder
Epothilone A_8 (7) R^8 = H; R^1, R^2 = Me

2. Epothilon der Formel



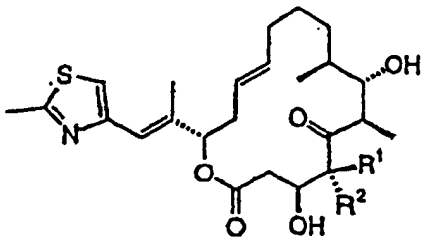
Epothilone C_1 (16) R^1 = H; R^2, R^3, R^4 = Me; R = H oder
Epothilone D_1 (17) R^1 = H; R^2, R^3, R^4 = Me; R = Me oder
Epothilone C_2 (18) R^2 = H; R^1, R^3, R^4 = Me; R = H oder
Epothilone D_2 (19) R^2 = H; R^1, R^3, R^4 = Me; R = Me

3. Epothilon der Formel



Epothilone C_8 (26) R^8, R^7 = H.

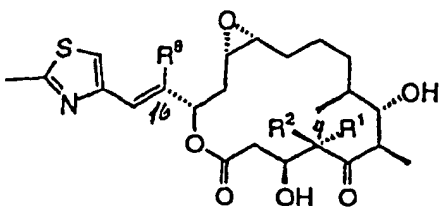
4. Epothilon der Formel



trans-Epothilone C_1 (28) R^1 = H; R^2 = Me oder
trans-Epothilone C_2 (29) R^2 = H; R^1 = Me

Claims

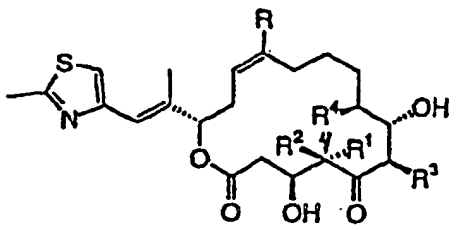
1. Epothilone of the formula



Epothilone A_1 (5) R^1 = H; R^2,R^8 = Me or

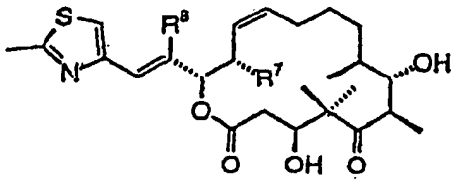
Epothilone A_2 (6) R^2 = H; R^1,R^8 = Me or
Epothilone A_8 (7) R^8 = H; R^1,R^2 = Me

2. Epothilone of the formula



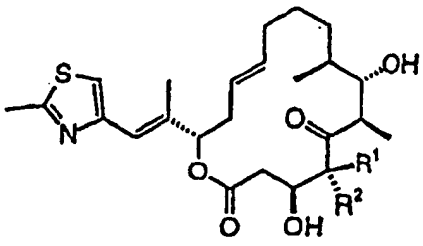
Epothilone C_1 (16) R^1 = H; R^2,R^3,R^4 = Me; R = H or
Epothilone D_1 (17) R^1 = H; R^2,R^3,R^4 = Me; R = Me or
Epothilone C_2 (18) R^2 = H; R^1,R^3,R^4 = Me; R = H or
Epothilone D2 (19) R^2 = H; R^1,R^3,R^4 = Me; R = Me

3. Epothilone of the formula



Epothilone C_8 (26) R^8, R^7 = H

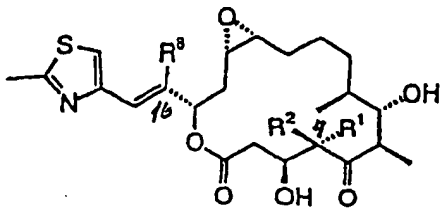
4. Epothilone of the formula



trans-Epothilone C_1 (28) R^1 = H; R^2 = Me or
trans-Epothilone C_2 (29) R^2 = H; R^1 = Me

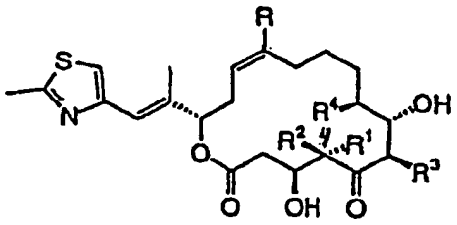
Revendications

1. Epothilone de la formule



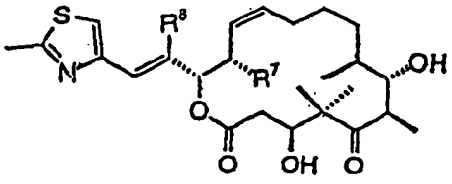
Epothilone A_1 (5) R^1 = H; R^2,R^8 = Me ou
Epothilone A_2 (6) R^2 = H; R^1,R^8 = Me ou
Epothilone A_8 (7) R^8 = H; R^1,R^2 = Me

2. Epothilone de la formule



Epothilone C_1 (16) R^1 = H; R^2,R^3,R^4 = Me; R = H ou
Epothilone D_1 (17) R^1 = H; R^2,R^3,R^4 = Me; R = Me ou
Epothilone C_2 (18) R^2 = H; R^1,R^3,R^4 = Me; R = H ou
Epothilone D_2 (19) R^2 = H; R^1,R^3,R^4 = Me; R = Me

3. Epothilone de la formule



Epothilone C_8 (26) R^8, R^7 = H

4. Epothilone de la formule

trans-Epothilone C_1 (28) R^1 = H; R^2 = Me ou
trans-Epothilone C_2 (29) R^2 = H; R^1 = Me

Fig. 1 Trennungsgang für

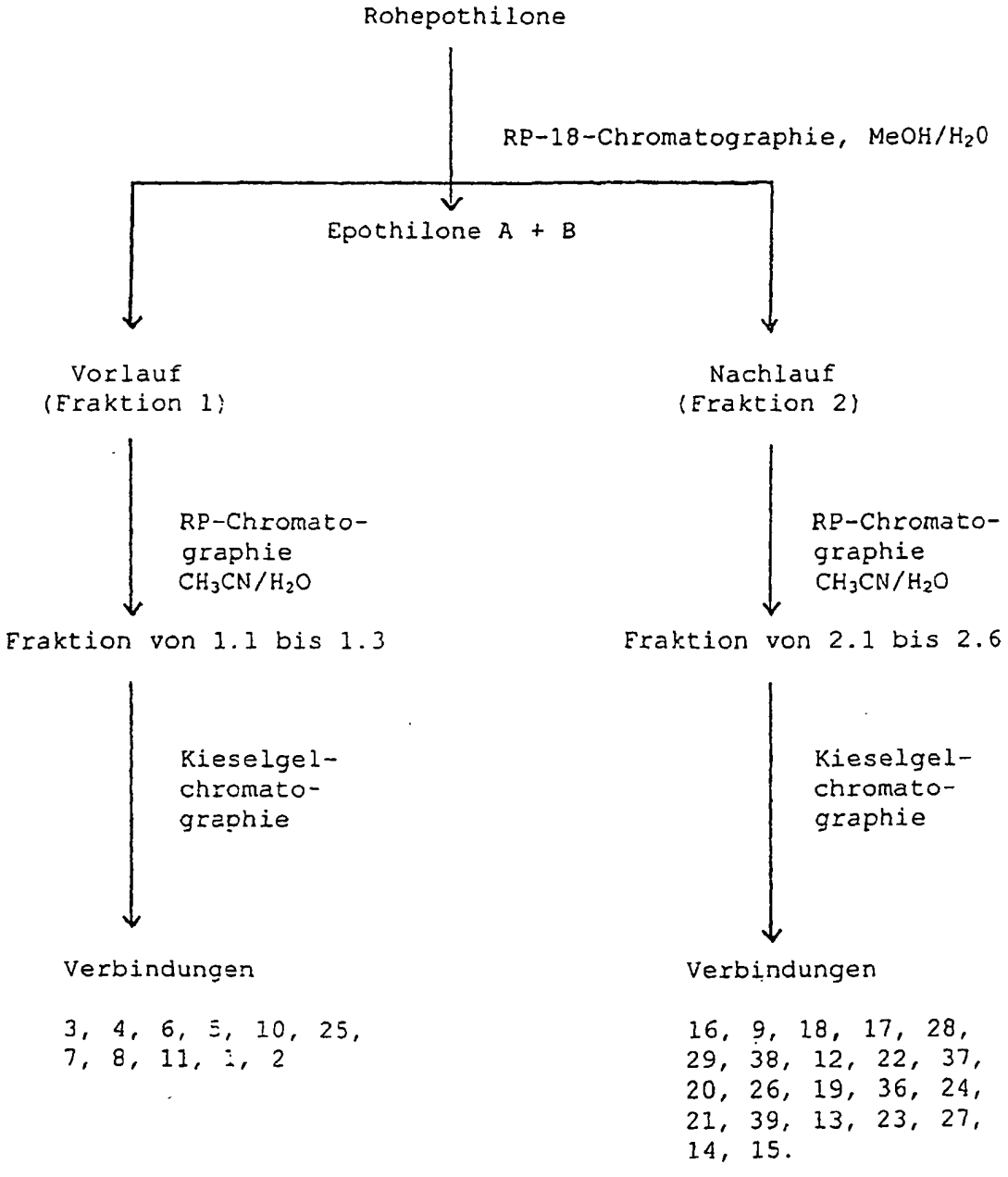
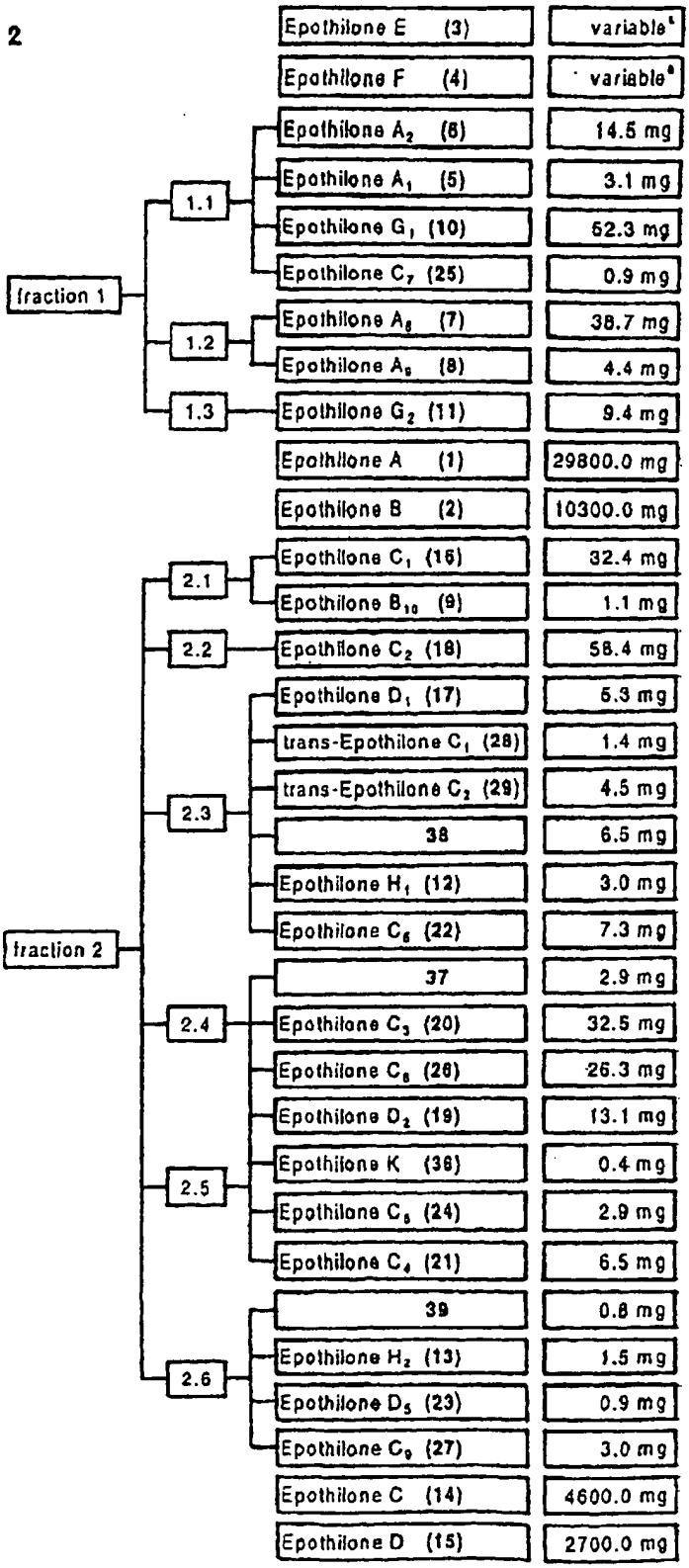


Fig. 2


Epothilone E (3)
variable[c]
Epothilone F (4)
variable[d]
Epothilone A2 (6)
14.5 mg
Epothilone A1 (5)
3.1 mg
Epothilone G1 (10)
52.3 mg
Epothilone C7 (25)
0.9 mg
Epothilone A6 (7)
38.7 mg
Epothilone A5 (8)
4.4 mg
Epothilone G2 (11)
9.4 mg
Epothilone A (1)
29800.0 mg
Epothilone B (2)
10300.0 mg
Epothilone C1 (16)
32.4 mg
Epothilone B10 (9)
1.1 mg
Epothilone C2 (18)
58.4 mg
Epothilone D1 (17)
5.3 mg
trans-Epothilone C1 (28)
1.4 mg
trans-Epothilone C2 (29)
4.5 mg
38
6.5 mg
Epothilone H1 (12)
3.0 mg
Epothilone C6 (22)
7.3 mg
37
2.9 mg
Epothilone C3 (20)
32.5 mg
Epothilone C8 (26)
26.3 mg
Epothilone D2 (19)
13.1 mg
Epothilone K (36)
0.4 mg
Epothilone C5 (24)
2.9 mg
Epothilone C4 (21)
6.5 mg
39
0.8 mg
Epothilone H2 (13)
1.5 mg
Epothilone D5 (23)
0.9 mg
Epothilone C9 (27)
3.0 mg
Epothilone C (14)
4600.0 mg
Epothilone D (15)
2700.0 mg
fraction 1
fraction 2
1.1
1.2
1.3
2.1
2.2
2.3
2.4
2.5
2.6